

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Noritaka KITAZAWA et al.  
Serial No: NEW Group: Unassigned  
Filed: May 2, 2001 Examiner: Unassigned  
For: CERTAIN QUINOLINE DERIVATIVES

**PRELIMINARY AMENDMENT**

Assistant Commissioner of Patent  
Washington, D.C. 20231

May 2, 2001

Sir:

Prior to initial examination of this divisional application, please amend the specification of the concurrently filed application as indicated below.

**IN THE SPECIFICATION:**

**On page 13, line 4, replace the paragraph, with the following new paragraph:**

1-{1-[4-(1-hydroxyethyl)phenethyl]piperidin-4-yl}indoline,

**On page 14, line 10, replace the paragraph, with the following new paragraph:**

1-{1-[2-hydroxyethoxy]phenethyl]piperidin-4-yl}indoline,

**On page 17, line 16, replace the paragraph, with the following new paragraph:**

1-[1-(t-butoxycarbonyl)piperidin-4-yl]-6-bromoindoline,

**On page 17, line 18, replace the paragraph, with the following new paragraph:**

1-[1-(t-butoxycarbonyl)piperidin-4-yl]-6-hydroxymethylindoline,

**On page 17, line 20, replace the paragraph, with the following new paragraph:**

1-[1-(t-butoxycarbonyl)piperidin-4-yl]-6-aminomethylindoline,

**On page 35, beginning at line 7 replace the paragraph, with the following new paragraph:**

(302) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(4-hydroxypiperidin-1-yl)carbonylmethylindole,

**On page 36, beginning at line 13 replace the paragraph, with the following new paragraph:**

(317) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-methoxypyridin-5-yl)carbonylindole,

**On page 39, beginning at line 1, replace the paragraph, with the following new paragraph:**

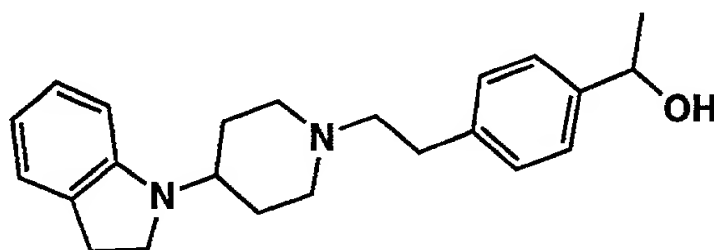
(347) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,3-dioxolan-2-yl)methylcarbamoylethylindole,

**On page 55, beginning at line 16 (bridging pages 55-56), replace the paragraph, with the following new paragraph:**

Among the 1,4-substituted cyclic amine derivatives (I) according to the present invention, compounds having structures other than those as defined in the above cases (1) to (5) can be produced by the same methods as the ones as will be described in Examples hereinafter.

**On page 194, beginning at line 22 (bridging pages 194-195), replace the paragraph, with the following new paragraph:**

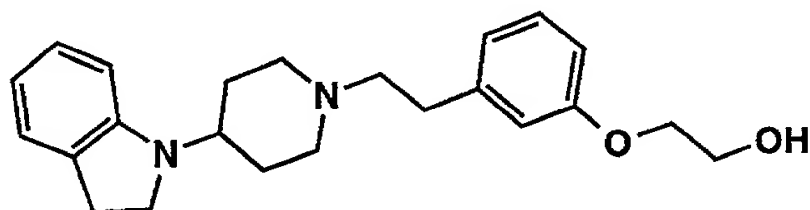
Example 25: Synthesis of 1-{1-[4-(1-hydroxyethyl)phenethyl]piperidin-4-yl}indoline



4-(1-Hydroxyethyl)phenethyl bromide (0.2 g) was treated as in Example 2 to give the title compound (0.044 g) as a yellow oil (yield: 12.6%).

**On page 213, beginning at line 16 (bridging pages 213-214), replace the paragraph, with the following new paragraph:**

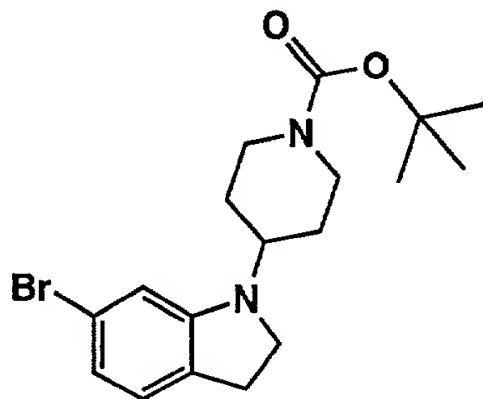
Example 43: Synthesis of 1-{1-[3-(2-hydroxyethoxy)phenethyl]piperidin-4-yl}indoline



3-[2-(t-Butyldimethylsilyloxy)ethoxy]phenethyl bromide (0.33 g) was treated as in Example 24 to give the title compound (0.197 g) as a yellow oil (yield: 53.8%).

**On page 274, beginning at line 4, replace the paragraph, with the following new paragraph:**

Example 88: Synthesis of 1-[1-(t-butoxycarbonyl)piperidin-4-yl]-6-bromoindoline

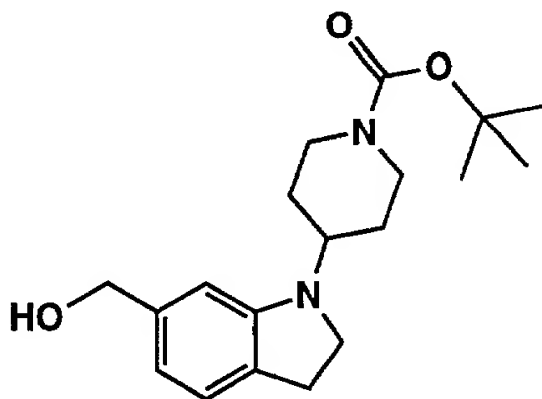


**On page 274, beginning at line 8, replace the paragraph, with the following new paragraph:**

Triacetoxylated sodium borohydride (11.7 g) was added to a mixture of 6-bromoindoline (8.3 g), 1-(t-butoxycarbonyl)-4-piperidone (10 g, [CAS Registry No. 7909-07-3]), acetic acid (14.9 g) and dichloroethane (200 ml) followed by stirring overnight. Then the reaction solution was concentrated under reduced pressure, and the pH value thereof was adjusted to 9 with ethyl acetate, an 8 N aqueous solution of sodium hydroxide and water and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (10.3 g) (yield: 64%).

**On page 275, beginning at line 5, replace the paragraph, with the following new paragraph:**

Example 89: Synthesis of 1-[1-(t-butoxycarbonyl)piperidin-4-yl]-6-hydroxymethylindoline



**On page 275, beginning at line 9 (bridging pages 275-276), replace the paragraph, with the following new paragraph:**

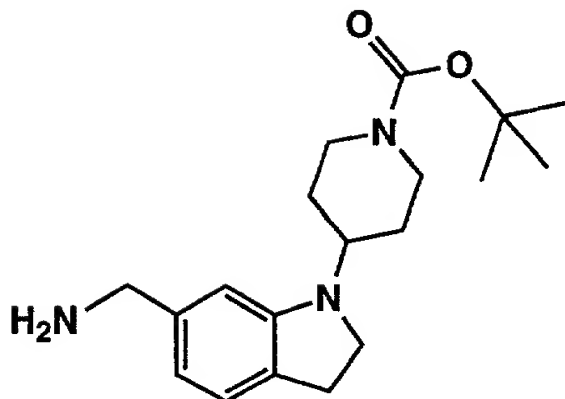
A 2.5 M solution (16 ml) of n-butyllithium in hexane was added dropwise at -78°C into a solution of 1-[1-(t-butoxycarbonyl)piperidin-4-yl]-6-bromoindoline (10 g) in tetrahydrofuran (250 ml) over 5 min. After 10 min, dimethylformamide (3.0 ml) was added and the resultant mixture was allowed to warm to room temperature. Next, a saturated aqueous solution of ammonium chloride and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue were added ethanol (50 ml) and sodium borohydride (1.0 g) and the resultant mixture was stirred at room temperature for 30 min. Then ice water and ethyl acetate were added to the reaction solution and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (7.9 g) (yield: 91%).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):

**On page 276, beginning at line 11, replace the paragraph, with the following new paragraph:**

Example 90: Synthesis of 1-[1-(t-butoxycarbonyl)piperidin-4-yl]-6-

aminomethylindoline



On page 276, beginning at line 16 (bridging pages 276-277), replace the paragraph, with the following new paragraph:

Under ice cooling, a solution of diethyl azodicarboxylate (4.6 g) in tetrahydrofuran (20 ml) was added dropwise into a solution of 1-[1-(t-butoxycarbonyl)piperidin-4-yl]-6-hydroxymethylindoline (7.9 g), triphenylphosphine (6.9 g) and phthalimide (3.9 g) in tetrahydrofuran (250 ml) and the resultant mixture was stirred at room temperature for 3 hr. After concentrating under reduced pressure, the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system). Then hydrazine hydrate (3.6 g) and ethanol (150 ml) were added thereto followed by heating under reflux for 2 hr. After ice cooling, the resulting crystalline precipitates were filtered off and the filtrate was concentrated under reduced pressure to give the title compound (8.3 g).

**On page 489, beginning at line 14 (bridging pages 489-490), replace the paragraph, with the following new paragraph:**

A solution of 1-{1-[2-(4-fluorophenyl)-2-hydroxyethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline (250 mg) in methylene chloride (5 ml) was cooled to -78°C and diethylaminosulfur trifluoride (DAST, 0.1 ml) was added thereto. Then the reaction solution was stirred at the same temperature for 45 min. After the completion of the reaction, saturated sodium bicarbonate was added to the reaction solution, which was then allowed to warm to room temperature under stirring. The reaction solution was extracted with ethyl acetate and the organic layer was dried over magnesium sulfate. After evaporating the solvent, the resulting residue was purified by silica gel column chromatography (hexane/hexane system) to give 1-{1-[2-(4-fluorophenyl)-2-fluoroethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline as an oil. This product was dissolved in ethyl acetate. After adding hydrochloric acid, the resulting salt was recrystallized from ethanol/ether to give the title compound (60 mg) (yield: 24%).  
m.p.: 227 - 229°C.

**On page 491, beginning at line 2, replace the paragraph, with the following new paragraph:**

4-Bromopyridine hydrochloride 7.04g (1.0 equivalent) was partitioned between an aqueous solution of sodium hydroxide and diethyl ether. The



organic layer was separated and dried over magnesium sulfate. Under nitrogen atmosphere, this solution was cooled to -78°C. Then a 1.6 M solution (25.0 ml, 1.0 equivalent) of n-butyllithium in hexane was added dropwise thereto and the resultant mixture was stirred for additional 30 min. Next, 6-methoxytetralone (7.049 g, 4.0 mmol) dissolved in tetrahydrofuran (50 ml) was added thereto and the resultant mixture was gradually warmed to room temperature while stirring continuously. After adding a saturated aqueous solution of ammonium chloride, the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was reprecipitated from chloroform/n-hexane to give the title compound (4.019 g) as a pale yellowish brown powder (yield: 39.4%).

**On page 537, beginning at line 4, replace the paragraph, with the following new paragraph:**

Example 302: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(4-hydroxypiperidin-1-yl)carbonylmethylindole

**On page 559, beginning at line 12, replace the paragraph, with the following new paragraph:**

Example 317: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-methoxypyridin-5-yl)carbonylindole

**On page 595, beginning at line 23, replace the paragraph, with the following new paragraph:**

Example 347: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,3-dioxolan-2-yl)methylcarbamoylmethylindolemethylindole

**On page 598, beginning at line 4, replace the paragraph, with the following new paragraph:**

Triacetoxylated sodium borohydride (15.0 g) was added under ice cooling to a liquid mixture of 6-bromoindoline (9.0 g), 1-(2-fluorophenethyl)piperidin-4-one (11.0 g) and acetic acid (12.5 ml) in 1,2-dichloroethane (140 ml). Then the reaction mixtures were stirred at room temperature overnight. The reaction mixtures were diluted with ethyl acetate (400 ml) and then an 8 N aqueous solution (70 ml) of sodium hydroxide was added thereto. The organic layer was separated, extracted with 5 N hydrochloric acid (100 ml) and then basified with an 8 N aqueous solution of sodium hydroxide. Then it was extracted with ethyl acetate and washed successively with water and brine. The ethyl acetate layer was dried over magnesium sulfate and the solvent was evaporated distilled off under reduced pressure to give the title compound (12.2 g) as a pale yellow solid (yield: 66.6 %).

**REMARKS**


The present amendments are made to correct typographical errors in the specification. Favorable action on and early allowance of the claims are respectfully requested.

If the Examiner has any questions concerning this application, he or she is invited to contact Mr. Richard Gallagher, Reg. No., 28,781 at (703) 205-8008.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees, particularly extension of time fees, required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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**MARKED UP VERSION OF AMENDMENTS**

**IN THE SPECIFICATION:**

Page 13

Line 4, change "1-{4-[(1-hydroxyethyl)phenethyl]piperidin-4-}" to --1-{1-[4-(1-hydroxyethyl)phenethyl]piperidin-4- --.

Page 14

Line 10, change "1-{3-[(2-hydroxyethoxy)phenethyl]piperidin-4-}" to --1-{1-[2-hydroxyethoxy)phenethyl]piperidin-4- --.

Page 17

Line 16, change "1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-" to --1-[1-(t-butoxycarbonyl)piperidin-4-yl]-6- --.

line 18, change "1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-" to --1-[1-(t-butoxycarbonyl)piperidin-4-yl]-6- --.

line 20, change "1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-" to --1-[1-(t-butoxycarbonyl)piperidin-4-yl]-6- --.

Page 35

Line 8, change "hydroxypiperidin-1-ylcarbonylmethyl)indole," to --hydroxypiperidin-1-yl)carbonylmethylindole,--.

Page 36

Line 14, change "methoxypyridin-5-ylcarbonyl)indole," to

--methoxypyridin-5-yl)carbonylindole,--.

Page 39

Line 2, change "dioxolan-2-ylmethyl)carbamoylemethylindole," to --  
dioxolan-2-yl)methylcarbamoylemethylindole,--.

Page 56

Line 1, change "(4)" to --(5)--.

Page 194 (counting the formula as one line)

Line 22, change "~~1-[4-[(1~~" to --1-[1-[4-(1- --.

Page 213 (counting the formula as one line)

Line 16, change "~~1-[3-[(2-~~" to --1-[1-[3-(2- --.

Page 274 (counting the formula as one line)

Line 4, change "~~1-[1-(4-t-~~" to --1-[1-(t- --.

line 8, change "~~1-(4-t-~~" to --1-(t- --.

Page 275 (counting the formula as one line)

Line 5, change "~~1-[1-(4-t-butoxycarbonyl)-~~" to --1-[1-(t-butoxycarbonyl)- --.

line 9, change "~~1-[1-(4-t-~~" to --1-[1-(t- --.

Page 276 (counting the formula as one line)

Line 11, change "~~1-[1-(4-t-~~" to --1-[1-(t- --.

line 16, change "~~1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-~~" to --1-[1-(t-  
butoxycarbonyl)piperidin-4-yl]-6- --.

Page 490

Line 10, delete "ethyl acetate" (second occurrence).

Page 491 (counting the formula as one line)

Line 2, change "7.04" to --7.04g--.

Page 537

Line 5, change "~~4-yl]-6-(4-hydroxypiperidin-1-ylcarbonylmethyl)indole~~" to --~~4-yl]-6-(4-hydroxypiperidin-1-yl)carbonylmethyl~~indole--.

Page 559

Line 13, change "~~4-yl]-6-(2-methoxypyridin-5-ylcarbonyl)indole~~" to --"4-yl]-6-(2-methoxypyridin-5-yl)carbonylindole--.

Page 595

Line 24, change "~~4-yl]-6-(1,3-dioxolan-2-ylmethyl)carbamo~~yl methylindole" to --"4-yl]-6-(1,3-dioxolan-2-yl)methylcarbamo~~yl~~methylindole--.

Page 598

Line 12, change "(ml) to --(100 ml)--.